FORM PTO-1390 (REV 10-94) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		9320.146USWO
		U S APPLICATION NO (If known, see 37 C F R 1 5) Unknown 10/009027
INTERNATIONAL APPLICATION NO. PCT/FR99/01340	INTERNATIONAL FILING DATE June 8, 1999	PRIORITY DATE CLAIMED None

TITLE OF INVENTION

NON-SOLID COMPOSITION FOR LOCAL APPLICATION

APPLICANT(S) FOR DO/EO/US

SHRIVASTAVA

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [ ] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US)
6. [X] A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.

8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

9. [X] An unsigned oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).

10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1 97 and 1.98
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. [X] A FIRST preliminary amendment.
    [ ] A SECOND of SUBSEQUENT preliminary amendment.

14. [ ] A substitute specification.

15. [ ] A change of power of attorney and/or address letter.

16. [X] Other items or information: Front page of PCT application as published, International Search Report; International Preliminary Examination Report; English translation of amended claims

U.S. APPLICATION NO (If known, see 37 C F R 1 5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
Unknown 10/009027	PCT/FR99/01340	9320.146USWO

17. [X] The following fees are submitted:	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492(a) (1)-(5)):		
Search Report has been prepared by the EPO or JPO **$890.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.492(a)(1)) **$710.00**		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) **$740.00**		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(3)) paid to USPTO **$1040.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$890.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	**$0**	

CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE		
Total claims	8	-20 =	0	X **$18.00**	**$0**	
Independent claims	2	-3 =	0	X **$84.00**	**$0**	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)				+ **$260.00**	**$0**	
TOTAL OF ABOVE CALCULATIONS =					**$890.00**	
Reduction by 1/2 for filing by small entity, if applicable. Small entity status is claimed pursuant to 37 CFR 1.27					**$445.00**	
SUBTOTAL =					**$445.00**	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1 492(f).				+	**$0**	
TOTAL NATIONAL FEE =					**$445.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property				+	**$0**	
TOTAL FEES ENCLOSED =					**$445.00**	
					Amount to be: refunded	**$0**
					charged	**$0**

a. [X] Check in the amount of $445.00 to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. _____ in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13-2725.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO
John J. Gresens
MERCHANT & GOULD
P.O. Box 2903
Minneapolis, MN 55402-0903

SIGNATURE: John J. Gresens

NAME: John J. Gresens

REGISTRATION NUMBER: 33,112

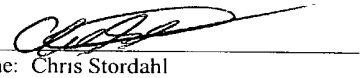
S/N unknown

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	SHRIVASTAVA	Docket No.:	9320.146USWO
Serial No.:	unknown	Filed:	concurrent herewith
Int'l Appln No.:	PCT/FR99/01340	Int'l Filing Date:	June 8, 1999
Title:	NON-SOLID COMPOSITION FOR LOCAL APPLICATION		

CERTIFICATE UNDER 37 CFR 1.10
'Express Mail' mailing label number: EV 037641360 US
Date of Deposit: December 6, 2001
I hereby certify that this correspondence is being deposited with the United States Postal Service 'Express Mail Post Office To Addressee' service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, P.O. Box 2327, Arlington, VA 22202.

By: 
Name: Chris Stordahl

PRELIMINARY AMENDMENT

Box PCT
Assistant Commissioner for Patents
P.O. Box 2327
Arlington, VA 22202

Dear Sir:

In connection with the above-identified application filed herewith, please enter the following preliminary amendment, which is based on the Article 34 amendments, based on claims amended in prosecution of the international application and published in the International Preliminary Examination Report, a copy of which is enclosed herewith (marked-up copy attached):

IN THE ABSTRACT

Insert the attached Abstract page into the application as the last page thereof.

IN THE SPECIFICATION

A courtesy copy of the present specification is enclosed herewith. However, the World Intellectual Property Office (WIPO) copy should be relied upon if it is already in the U.S. Patent Office.

IN THE CLAIMS

Please cancel claims 7 and 9.

Please amend the following claims:

4. (Amended) Non-solid formulation for local application according to claim 1 characterised in that the active ingredient concentration gives it an osmotic power greater than 500 milliosmoles.

5. (Amended) Non-solid formulation for local application according to claim 1 characterised in that its active ingredient concentration is such that the quantity by volume of the diluent (solvent) is less than 20%.

6. (Amended) Non-solid formulation for local application according to claim 1 characterised in that at least one osmotically active solution with respect to blood plasma is associated with an antiseptic product or a healing product for the treatment of aphthae and skin wounds.

8. (Amended) Non-solid formulation according to claim 1, characterised in that it consists of a pharmaceutical or oral hygiene formulation.

REMARKS

The above preliminary amendment is made to remove multiple dependencies from claims 4, 5, 6 and 8.

A new abstract page is supplied to conform to that appearing on the publication page of the WIPO application, but the new Abstract is typed on a separate page as required by U.S. practice.

Applicants respectfully request that the preliminary amendment described herein be entered into the record prior to calculation of the filing fee and prior to examination and consideration of the above-identified application.

If a telephone conference would be helpful in resolving any issues concerning this communication, please contact Applicants' primary attorney-of record, John J. Gresens (Reg. No. 33,112), at (612) 371.5265.

Respectfully submitted,

MERCHANT & GOULD P.C.
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Dated: December 6, 2001

By ____________________
John J. Gresens
Reg. No. 33,112

JJG/tvm

ABSTRACT

Title: NON-SOLID COMPOSITION FOR LOCAL APPLICATION

The invention concerns a composition, in particular a non-solid pharmaceutical composition for local application comprising, as active principle, at least glycerol or a concentrated solution of glycerol, saccharose, sorbitol or mannitol, the active principle concentration of said composition being osmotically active towards plasma.

MARKED-UP COPY

4. (Amended) Non-solid formulation for local application according to [any of claims 1 to 3] claim 1 characterised in that the active ingredient concentration gives it an osmotic power greater than 500 milliosmoles.

5. (Amended) Non-solid formulation for local application according to [any of claims 1 to 4] claim 1 characterised in that its active ingredient concentration is such that the quantity by volume of the diluent (solvent) is less than 20%.

6. (Amended) Non-solid formulation for local application according to [any of claims 1 to 5] claim 1 characterised in that at least one osmotically active solution with respect to blood plasma is associated with an antiseptic product or a healing product for the treatment of aphthae and skin wounds.

8. (Amended) Non-solid formulation according to [any of claims 1 to 6] claim 1, characterised in that it consists of a pharmaceutical or oral hygiene formulation.

[redacted]

#3

INDEPENDENT INVENTOR(S)

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 C.F.R. 1.9(f)) - INDEPENDENT INVENTOR

As a below named inventor, I hereby declare that I qualify as an independent inventor as defined in 37 C.F.R. 1.9(c) for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, United States Code, to the Patent and Trademark Office with regard to the invention entitled NON-SOLID COMPOSITION FOR LOCAL APPLICATION described in

a) ☐ the specification filed herewith.
b) ☐ provisional application serial no. _____, filed _____.
c) ☒ non-provisional application serial no. _____, filed _____.
d) ☐ patent no. _____, issued _____.

I have not assigned, granted, conveyed or licensed and am under no obligation under contract or law to assign, grant, convey or license, any rights in the invention to any person who could not be classified as an independent inventor under 37 C.F.R. 1.9(c) if that person has made the invention, or to any concern which would not qualify as a small business concern under 37 C.F.R. 1.9(d) or a nonprofit organization under 37 C.F.R. 1.9(e).

Each person, concern or organization to which I have assigned, granted, conveyed, or licensed or am under obligation under contract or law to assign, grant, convey, or license any rights in the invention is listed below:

a) ☒ no such person, concern, or organization
b) ☐ persons, concerns or organizations listed below*

NAME _____
ADDRESS _____
a) ☐ INDIVIDUAL b) ☐ SMALL BUSINESS CONCERN c) ☐ NONPROFIT ORGANIZATION

NAME _____
ADDRESS _____
a) ☐ INDIVIDUAL b) ☐ SMALL BUSINESS CONCERN c) ☐ NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 C.F.R. 1.27(g)(2))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereof, or any patent to which this verified statement is directed.

Ravi Shrivastava		
NAME OF INVENTOR	NAME OF INVENTOR	NAME OF INVENTOR
Signature of Inventor	Signature of Inventor	Signature of Inventor
Date 14.01.2002	Date	Date

LIQUID COMPOSITION FOR TOPICAL APPLICATION

This invention relates to a new liquid or viscous composition notably pharmaceutical containing a hypertonic solution or glycerin, and their use for the treatment of oral ulcers and the superficial injuries.

The development of lesions in the form of ulcers in the buccal cavity, and occasionally on other parts of the body is a very common phenomenon. Most individuals are susceptible to develop oral ulcers and small topical injuries. Although ulcers do not constitute a fully fledged illness, they cause considerable pain and discomfort.

From physiopathological point of view, an ulcer can be considered as a localised breach of the superficial zones of the skin or mucosa. This injury exposes the underlying and deeper parts of the ulcer to more severe traumatisms, which is manifested by rupture of localised blood vessels and degradation of deeper layers of the tissue. These minor injuries are exposed to micro-organisms, particularly the streptococci and staphylococci responsible for secondary infections, which leads to secondary lesions in the form of oral ulcers.

The development of such lesions is often associated with traumatic injuries and itches but the formation of oral ulcers on the mucosa may also be related to other factors, which are not yet fully understood. In addition to the traumatic lesions, the development of blisters and oral ulcers can also be due to certain elements in the food, which alter mucosal surface. The deficiency of certain vitamins, such as the vitamin A is also responsible for mucous membrane fragility, which breaks easily following small injuries.

Clinically, the ulcers and superficial injuries are small lesions of the mucosa or epidermis (a few millimetres to a few centimetres), purplish or yellowish in colour, that let open the underlying tissue layers and the blood vessels. These lesions constitute an ideal site for bacterial proliferation. The presence of pyogenic bacteria is a common phenomenon. The body defence mechanisms and the tissue healing processes are immediately activated after the

appearance of tissue injury and start the healing process. The immunity system fights against bacterial growth finally to prepare the damaged zone for regeneration.

Although the healing process is relatively rapid for skin lesions, it may take minimum seven to ten days to completely heal an oral ulcer. This prolonged healing process is related to the fact that oral ulcers are constantly in contact with food, which contains non-pathogenic micro-organisms. Thus, the lesion is constantly exposed to bacteria, which are ready to multiply in a favourable environment. The constant movements of mouth, for example while speaking, equally increases healing time and delays injury repair.

All currently available treatments are directed to stop or reduce bacterial growth in the lesion but have no effect on the tissue regeneration process necessary for a rapid healing. Most of the available treatments for ulcers contain antibiotics or antiseptic agents. Often these treatments are for topical application.

In case of severe infection, antibiotics are used orally. The major disadvantage of these treatments is that they act only on the secondary bacterial infection but have no effect on the tissue regeneration. Very often, people have the tendency to scrape affected zone, which provokes an inflammation and can aggravate the extension of lesion. Another major disadvantage of currently available treatments is that they do not reduce the healing period, people continue suffering from pain and increase in the size of the lesion.

Therefore, an ideal treatment for oral ulcers must possess the following three major qualities:

- Eliminate micro-organisms present inside the lesion, finally to prepare a favourable ground for cellular growth,
- Accelerate tissue regeneration to stimulate healing and to minimise recovery period,
- Should be non-toxic and should be free of side-effects.

Till today, no product with these three properties of removing bacteria from the lesion, stimulating healing and being non-toxic, was discovered.

The glycerin or concentrated solutions, for example the concentrated sugar solutions were often used as preservatives, for example in jams, or as excepient but no pharmacological properties, particularly for the treatment of ulcers were assigned to these products. Surprisingly, we discovered that the bacteria can be easily removed from the ulcer in a very short period of time by the application of a concentrated osmotically active solution compared to the plasma, and that the healing period can be considerably reduced by adding a substance capable to stimulate cell proliferation.

The present invention therefore concerns a non-solid and preferably a liquid composition for topical application containing glycerol or a concentrated solution of glycerol, sucrose, sorbitol or mannitol as active product, the concentration of such a non-solid composition being osmotically active compared to plasma particularly the blood plasma.

In the preferred form of the preparation, this non-solid composition is a pharmaceutical preparation.

According to current invention, the term non-solid is applied to the liquid as well as gluey (viscous) preparations.

Our observations show that pure glycerol or a concentrated solution of sucrose, sorbitol, mannitol or glycerin (glycerol) applied on an open superficial injury induce accelerated flow of plasma from the injury and stimulate lesion healing.

The increased outward plasma flow is a result of osmotic process between the inner and the outer parts of the wound. According to the law of diffusion, the glycerol or any hypertonic solution tries to penetrate into the tissue. However, due to the large size of molecules in these solutions, their penetration into the tissue is not possible. On the contrary,

the highly permeable hypotonic plasma around the damaged capillaries of the injury drains out to balance the osmetic equilibrium. The topical application of a hypertonic solution on an injured tissue therefore produces exudation of a large amount of plasma from the wound. During this process, the micro-organisms present at the level of the lesion are eliminated along with the flow of plasma which immediately reduces bacterial load inside the wound. Therefore the concentrated solutions allow to drain superficial injuries and ulcers.

This plasma exudation equally brings many immunity factors (immunoglobins, complement system, leukocytes) participating in microbial elimination, which prepares a favourable ground for ulcer healing.

Furthermore, the glycerol, the concentrated solutions of sucrose, sorbitol, mannitol or glycerine (glycerol) are very less toxic or at all non-toxic for health and can be used orally without any side-effect.

The preferential compositions according to the present invention concerns use of pure glycerol as active principle. Non-solid compositions of sucrose or mannitol can also be preferred.

Under optimal conditions of preparation according to this invention, the concentration of active principle in the non-solid composition should allow to obtain a solution having osmotic concentration superior to plasma: minimum 300 milliosmoles (mOsm), preferably superior to 500 mOsm, notably superior to 800 mOsm and specifically superior to1 mOsm. This cosmetic capacity is assigned through the incorporation of active principle in the solution at a concentration of minimum 30%, preferably minimum 60%, particularly 90% and specifically minimum 95%,the remaining osmotic capacity can be obtained by the addition of other osmotically active ingredients.

Under preferential conditions of preparation, the concentration of active principle in the non-solid composition is such that the volume of diluant (solvent) is less than 70%, preferably less than 40%, notably less than 20%, preferably less than 10%.

The association of these osmotically active products with antibiotics or antiseptic, either natural or synthetic, helps to enhance antibacterial properties. The association of these osmotically active substances with another ingredient capable to stimulate cell proliferation equally helps to accelerate the speed of healing.

For these reasons, the current invention also concerns a non-solid composition as explained above in which an osmotically active substance is associated with at least one antiseptic or a product capable to stimulate cell growth. Such an association represents an excellent remedy for the treatment of ulcers, superficial injuries, and burns, for postoperative care and to accelerate healing with minimum scar tissue formation.

Non-solid compositions according to present invention can be mixed with different substances capable to stimulate cell proliferation particularly with plant extracts used traditionally or not for dermatological ailments (Mimosa tenuiflora, Quercus, Aesculus hippocastanum, Geranium robertianum, Cupressus sempervirens, Vitis vinifera, Ribes nigrum, Centella asiatica, Matricaria Chamomilla and particularly the Alchemilla vulgaris) or with any other substance with « growth factor » type activity (example : escine, tannins, procynadolic, oligomers, mimosides) or with a bacteriostatic or bacteriocidal antibiotics (examples papaïne, geranine).

These compositions particularly pharmaceuticals, can be liquid or viscous and can be presented in pharmaceutical forms commonly employed in human medicine, for example elongated tubes containing solutions or sprays manufactured employing traditional methods.

The active principles can be incorporated in any commonly used excipient such as the aqueous or non-aqueous excipients, different humidifying agents the preservatives and the thickening agents.

This invention also concerns the use of glycerol or the concentrated solutions of glycerol sucrose, sorbitol or mannitol in osmotically active concentrations compared to the plasma for a method of treatment for human or animal body, i.e. as a drug.

The drugs according to the present invention can be used for the preventive or curative treatment of ulcers. They can also be used for the treatment of ulcers on the mucosa or skin epidermis other than blisters.

The usual dose varies according to the person treated and according to the type of injury, for example, 2 to 6 topical oral applications of 2 drops of the composition given in the example number 3 on each ulcer per day for a period of 3 days.

The current invention also includes the method of preparation of the compositions given above, characterised by the mixing of an osmotically active solution with an pharmaceutically acceptable excipient.

This invention is principally related to the use of glycerol or a concentrated solution of glycerol, sucrose, sorbitol or mannitol, in osmotically active concentrations compared to plasma, to produce a drug directed to treat small lesions on the mucosa or epidermis, notably the ulcers.

The preferential conditions of preparation of such non-solid and preferably liquid compositions are given below which are also applied to other formulations given in this patent.

The following examples illustrate the patent request.

10-ml tubes with a 4cm long canula were prepared by formulating the following composition :

Example 1

Water 60-ml

Sorbitol 40g

Shake to obtain a clear solution

Example 2

Water 50-ml

Glycerol 50-ml

Example 3

10-ml tubes with a 4cm long canula were prepared by weighing the following composition:

Water	45%
Xanthan gum	0.5%
Methyl parahydroxy benzoate	0.15%
Hydroalcoholic extract of Lady's Mantle*	5.0%
Blackcurrant perfume	0.43%
Glycerol qsp	100%

*Obtained from Biosphère, France :150 g dried leaves mixed with 500-ml water and 500-ml ethanol.

Example 4

Glycerin	97-ml

Dried extract of Alchemilla vulgaris : 3g

Mix.

Example 5

Glycerol	90%
Blackcurrant extract	9%
Extract of Azadarachta indica	1%

Mix.

Example 6

Glycerin	96.5%
Extract of Alchemilla vulgaris	3.0%
Extract of Azadirachta indica	0.5%

Example 7

Different capacity tubes were prepared according to the following formula :

Extract of horse chestnut	8.1%
Cypress extract	5.0%
Geranium robertianum extract	4.0%
Escin	0.3%
Papain	0.1%
Carbomer	0.5%
Alcohol	4.0%

Phenonip		0.5%
PEG-7 Glyceryl cocoate		3.0%
Glycerol		30%
Water	qsp	100%

Example 8

Different capacity tubes were prepared according to the following formula :

Extract of Alchemilla vulgaris	9.8%
Vitis vinifera	2.0%
Mimosa tenuiflora	5.0%
Carbomer	0.4%
PEG-7 Glyceryl cocoate	2.0%
Phenonip	0.5%
Triethanolamine	0.2%
Fragrance	0.2%
Glycerol	10-40%
Water	qsp 100%

Example 9

Different capacity tubes were prepared according to the following formula :

Quercus extract	0.5%
Escine	0.1%
Azadirachta indica	1.1%
Methyl parahydroxybenzoate	0.15%
Xanthan Gum	0.5%

Balckcurrant extract	0.43%
Glycerol	50%
Water	qsp 100%

PHARMACOLOGICAL STUDIES

30 rats (IOPS, IFFA-CREDO 200+/- 20g) were shaved (3x3 cm) on the right side of the back. A wound of 0.4x0.4 cm was created with the help of a scissors and knife. 30 minutes after wounding, clotted blood was removed and 0.2-ml of glycerine containing 3% Alchemilla vulgaris extract was applied on the wounds of 10 rats. Other 10 rats received 0.2-ml distilled water.

The complete recovery time and the healing index were calculated every day over 10 days. The recovery time was reduced by 48% in glycerine – 3% Alchemilla vulgaris treated group with a healing index of 2.1 in the treated group compared to 3.3 in the control group.

With glycerin alone, the wound healing time was reduced by 26% with a healing index of 2.7. These results show that glycerin alone helps wound healing but the association of glycerin with a product capable to stimulate cellular mitotic activity markedly enhances the speed of healing.

The effect of different plant extracts on the rate of epithelial cell proliferation was determined *in-vitro.* Bovine kidney cells (MDBK) were cultured in 96 well tissue culture micro- plated (10^5 cells / ml ; 100µl/ well). Different concentrations of plant extracts were added to the culture medium on day0 (n= 16 / dilution). Cells were incubated for 72 hours (37°C- 5% CO_2° and total number of cells was determined after trypsinization by MTT staining.

Only 5 out of 26 plant extracts tested showed activity to stimulate cell proliferation in the following order: Alchemilla vulgaris, Mimosa tenuiflora, Quercus, Aesculus hippocastanum, Geranium robertianum, Cupresus sempervirens, Vitis vinifera, Ribes nigrum.

CLINICAL STUDY

10-ml tubes were prepared, containing either a solution of 97% glycerin with 3% hydroglycerinated extract of Alchemilla vulgaris (3%dried plant extract w/w) as given in the example 4, or a preparation containing 97% ethyl alcohol (96%) and 3% hydroalcoholic extract of Alchemilla vulgaris (3% dried extract w/w).

18 subjects having problems of oral ulcers were included in a pilot clinical trial. 8 conrol subjects tested product containing hydroalcoholic extract while 10 other participants received the product with hydroglycerinated extract. 2 drops of the product were applied 3 times a day after meals up to complete ulcer healing. The time required for complete healing was determined in the two groups.

The mean healing period was 2.7 days in the group treated with hydroglycerinated extract compared to 6.3 days in the controls.

The use of osmetically active substances or glycerin, alone or inassociation with other ingredients capable to stimulate cellular mitotic activity, stimulate cell proliferation, superficial wound healing and notably oral ulcer recovery.

ART 34 AMDT

CLAIMS

1. Non-solid formulation for local application for the treatment of aphthae and skin wounds characterised in that it comprises, as an active ingredient, glycerol and/or sucrose and/or sorbitol and/or mannitol giving it an osmotic power greater than that of blood plasma (greater than 300 milliosmoles), and a product stimulating cell multiplication composed of an Alchemilla vulgaris extract.

2. Non-solid formulation for local application according to claim 1, characterised in that said active ingredient is glycerol.

3. Non-solid formulation for local application according to claim 1, characterised in that said active ingredient is sorbitol or mannitol.

4. Non-solid formulation for local application according to any of claims 1 to 3 characterised in that the active ingredient concentration gives it an osmotic power greater than 500 milliosmoles.

5. Non-solid formulation for local application according to any of claims 1 to 4 characterised in that its active ingredient concentration is such that the quantity by volume of the diluent (solvent) is less than 20%.

6. Non-solid formulation for local application according to any of claims 1 to 5 characterised in that at least one osmotically active solution with respect to blood plasma is

associated with an antiseptic product or a healing product for the treatment of aphthae and skin wounds.

7. Non-solid formulation for local application according to any of claims 1 to 6, characterized in that the product stimulating cell proliferation is an an Alchemilla vulgaris extract.

8. Non-solid formulation according to any of claims 1 to 6, characterised in that it consists of a pharmaceutical or oral hygiene formulation.

9. Use of glycerol in an osmotically active concentration with respect to blood plasma, in association with a product stimulating cell proliferation to obtain a formulation intended for the treatment of mouth ulcers and skin disorders.

10. Use of glycerol, in an osmotically active concentration with respect to blood plasma in association with an Alchemilla vulgaris plant extract to obtain a formulation intended for the treatment of mouth ulcers and skin disorders.

(12) DEMANDE INTERNATIONALE PUBLIÉE EN VERTU DU TRAITÉ DE COOPÉRATION EN MATIÈRE DE BREVETS (PCT)

(19) Organisation Mondiale de la Propriété Intellectuelle
Bureau international

(43) Date de la publication internationale
14 décembre 2000 (14.12.2000)

PCT

(10) Numéro de publication internationale
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(21) Numéro de la demande internationale:
PCT/FR99/01340

(22) Date de dépôt international: 8 juin 1999 (08.06.1999)

(25) Langue de dépôt: français

(26) Langue de publication: français

(71) Déposant et
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(81) États désignés *(national)*: AU, BR, CA, CN, JP, US.

(84) États désignés *(régional)*: brevet européen (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

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En ce qui concerne les codes à deux lettres et autres abréviations, se référer aux "Notes explicatives relatives aux codes et abréviations" figurant au début de chaque numéro ordinaire de la Gazette du PCT.

WO 00/74668 A1

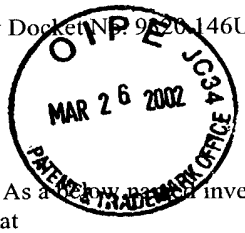
(54) Title: NON-SOLID COMPOSITION FOR LOCAL APPLICATION

(54) Titre: COMPOSITION NON SOLIDE POUR APPLICATION LOCALE

(57) Abstract: The invention concerns a composition, in particular a non-solid pharmaceutical composition for local application comprising, as active principle, at least glycerol or a concentrated solution of glycerol, saccharose, sorbitol or mannitol, the active principle concentration of said composition being osmotically active towards plasma.

(57) Abrégé: Composition notamment pharmaceutique non solide pour application locale comprenant, à titre de principe actif, au moins du glycérol ou une solution concentrée de glycérol, de saccharose, de sorbitol ou de mannitol, la concentration en principe actif de ladite composition étant osmotiquement active vis-à-vis du plasma.

Attorney Docket No. 9220.146USWO



MERCHANT & GOULD P.C.

United States Patent Application

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that

I verily believe I am the original, first and sole inventor (if only one name is listed below) or a joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: NON-SOLID COMPOSITION FOR LOCAL APPLICATION

The specification of which
a. ☐ is attached hereto
b. ☒ was filed on as application serial no. and was amended on (if applicable) (in the case of a PCT-filed application) described and claimed in international no. PCT/FR99/01340 filed June 8, 1999 and as amended on June 26, 2001 (if any), which I have reviewed and for which I solicit a United States patent.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119/365 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on the basis of which priority is claimed:

a. ☒ no such applications have been filed.
b. ☐ such applications have been filed as follows:

FOREIGN APPLICATION(S), IF ANY, CLAIMING PRIORITY UNDER 35 USC § 119			
COUNTRY	**APPLICATION NUMBER**	**DATE OF FILING (day, month, year)**	**DATE OF ISSUE (day, month, year)**
ALL FOREIGN APPLICATION(S), IF ANY, FILED BEFORE THE PRIORITY APPLICATION(S)			
COUNTRY	**APPLICATION NUMBER**	**DATE OF FILING (day, month, year)**	**DATE OF ISSUE (day, month, year)**

I hereby claim the benefit under Title 35, United States Code, § 120/365 of any United States and PCT international application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. APPLICATION NUMBER	DATE OF FILING (day, month, year)	STATUS (patented, pending, abandoned)

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below:

U.S. PROVISIONAL APPLICATION NUMBER	DATE OF FILING (Day, Month, Year)

I acknowledge the duty to disclose information that is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, § 1.56 (reprinted below):

§ 1.56 Duty to disclose information material to patentability.

(a) A patent by its very nature is affected with a public interest. The public interest is best served, and the most effective patent examination occurs when, at the time an application is being examined, the Office is aware of and evaluates the teachings of all information material to patentability. Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section. The duty to disclose information exists with respect to each pending claim until the claim is canceled or withdrawn from consideration, or the application becomes abandoned. Information material to the patentability of a claim that is canceled or withdrawn from consideration need not be submitted if the information is not material to the patentability of any claim remaining under consideration in the application. There is no duty to submit information which is not material to the patentability of any existing claim. The duty to disclose all information known to be material to patentability is deemed to be satisfied if all information known to be material to patentability of any claim issued in a patent was cited by the Office or submitted to the Office in the manner prescribed by §§ 1.97(b)-(d) and 1.98. However, no patent will be granted on an application in connection with which fraud on the Office was practiced or attempted or the duty of disclosure was violated through bad faith or intentional misconduct. The Office encourages applicants to carefully examine:

(1) prior art cited in search reports of a foreign patent office in a counterpart application, and

(2) the closest information over which individuals associated with the filing or prosecution of a patent application believe any pending claim patentably defines, to make sure that any material information contained therein is disclosed to the Office.

(b) Under this section, information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and

(1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or

(2) It refutes, or is inconsistent with, a position the applicant takes in:

(i) Opposing an argument of unpatentability relied on by the Office, or

(ii) Asserting an argument of patentability.

A prima facie case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability.

(c) Individuals associated with the filing or prosecution of a patent application within the meaning of this section are:

(1) Each inventor named in the application:

(2) Each attorney or agent who prepares or prosecutes the application; and

(3) Every other person who is substantively involved in the preparation or prosecution of the application and who is associated with the inventor, with the assignee or with anyone to whom there is an obligation to assign the application.

(d) Individuals other than the attorney, agent or inventor may comply with this section by disclosing information to the attorney, agent, or inventor.

(e) In any continuation-in-part application, the duty under this section includes the duty to disclose to the Office all information known to the person to be material to patentability, as defined in paragraph (b) of this section, which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

[redacted]

I hereby appoint the following attorney(s) and/or patent agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected herewith:

Albrecht, John W.	Reg. No. 40,481	Leonard, Christopher J.	Reg. No. 41,940
Ali, M. Jeffer	Reg. No. 46,359	Liepa, Mara E.	Reg. No. 40,066
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Berns, John M.	Reg. No. 43,496	McIntyre, Jr., William F.	Reg. No. 44,921
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Daignault, Ronald A.	Reg. No. 25,968	Pytel, Melissa J.	Reg. No. 41,512
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Doscotch, Matthew A.	Reg No. P-48,957	Schmaltz, David G.	Reg. No. 39,828
Edell, Robert T.	Reg. No. 20,187	Schuman, Mark D.	Reg. No. 31,197
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Jardine, John S.	Reg. No. P-48,835	Weaver, Paul L.	Reg. No. 48,640
Johns, Nicholas P.	Reg. No. 48,995	Welter, Paul A.	Reg. No. 20,890
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Kaseburg, Frederick A.	Reg. No. 47,695	Wier, David D.	Reg. No. P-48,229
Kettelberger, Denise	Reg. No. 33,924	Williams, Douglas J.	Reg. No. 27,054
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Knearl, Homer L.	Reg. No. 21,197	Witt, Jonelle	Reg. No. 41,980
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Lacy, Paul E.	Reg. No. 38,946	Young, Thomas	Reg. No. 25,796
Larson, James A.	Reg. No. 40,443	Zeuli, Anthony R.	Reg. No. 45,255

I hereby authorize them to act and rely on instructions from and communicate directly with the person/assignee/attorney/firm/ organization who/which first sends/sent this case to them and by whom/which I hereby declare that I have consented after full disclosure to be represented unless/until I instruct Merchant & Gould P.C. to the contrary.

I understand that the execution of this document, and the grant of a power of attorney, does not in itself establish an attorney-client relationship between the undersigned and the law firm Merchant & Gould P.C., or any of its attorneys.

Please direct all correspondence in this case to Merchant & Gould P.C. at the address indicated below:

Merchant & Gould P.C.
P.O. Box 2903
Minneapolis, MN 55402-0903

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2	**Full Name Of Inventor**	**Family Name** Shrivastava	**First Given Name** Ravi	**Second Given Name**
0	**Residence & Citizenship**	**City** Cebazat FR	**State or Foreign Country** France	**Country of Citizenship** France
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Signature of Inventor 201:			**Date:**	14.01.2002